Notice of Allowability	Application No.	Applicant(s)	
	09/621,592	JACKOWSKI, GEORGE	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the telephone interview of 3/23/04*.

2. ☒ The allowed claim(s) is/are *21, 23-33, 41-45, and 47-59 (re numbered 1-30 respectively)*.

3. ☒ The drawings filed on *09 February 2004* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *attached* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

3. Authorization for this examiner's amendment was given in a telephone interview with Helen Lee (Reg. No. 39,270) on 3/23/04.

In the claims:

1-20. (canceled)

21. (currently amended): A method for determining the occurrence of a cerebral event and differentially diagnosing between an ischemic cerebral event and a hemorrhagic cerebral event comprising:

a. analyzing a body fluid of a patient to detect presence and concentration level of ischemic marker proteins, said ischemic marker proteins consisting of myelin basic protein (MBP), the beta isoform of S100 protein (S100), and neuronal specific enolase (NSE), said analyzing comprising contacting said MBP, the beta isoform of S100 ~~or~~ and NSE with a reagent capable of detecting said marker proteins, detecting each of said marker proteins, and removing reagent that does not detect said marker proteins,

b. analyzing a body fluid of said patient to detect presence and concentration level of a brain endothelial cell membrane protein, said analyzing comprising contacting said brain endothelial cell membrane protein with a reagent capable of detecting

said endothelial cell membrane protein, detecting said endothelial cell membrane protein, and removing reagent that does not detect said brain endothelial cell membrane protein,

c. comparing the concentration level of each protein detected in steps (a) and (b) to specific threshold values to determine the presence of statistically significant concentrations thereof,

d. assessing patient condition by comparing said presence or absence of statistically significant concentrations of said protein in accordance with an analytical flowchart; and

e. determining whether the patient condition assessed in step (d) is an ischemic cerebral event or an hemorrhagic cerebral event,

wherein if ~~MBP, S100, NSE and brain endothelial cell membrane proteins are assessed in steps (a) and (b), and~~ only said NSE is elevated, ~~then said patient condition is an ischemic cerebral event;~~ or if ~~MBP, S100, NSE and brain endothelial cell membrane protein are assessed in steps (a) and (b), and~~ only said brain endothelial cell membrane protein is elevated, ~~then said patient condition is an ischemic cerebral event;~~ or if S100 is present alone or along with any of NSE, MBP or a brain endothelial cell membrane, ~~then said patient condition is an ischemic cerebral event; or if NSE along with any of MBP, S100 or a brain endothelial cell membrane protein are present, then said patient condition is an ischemic cerebral event; or if brain endothelial cell membrane protein, with any of MBP, NSE, or S100 are present, then said patient condition is an ischemic cerebral event; or if S100 is present with elevated NSE and normal levels of brain endothelial cell membrane protein, then said patient condition is an ischemic cerebral event; or if S100 is present alone, or along with elevated NSE or brain endothelial membrane protein,~~ then said patient condition is indicative of an ischemic cerebral event; ~~or wherein if~~ unless MBP is present at a level 200 times normal or greater, ~~then said patient condition is a hemorrhagic cerebral event;~~ or

unless ~~if~~ S100 and NSE levels are elevated, and MBP and brain endothelial membrane protein levels are normal, then said patient condition is indicative of a hemorrhagic cerebral event~~; or if S100 and MBP are elevated, then said patient condition is a hemorrhagic cerebral event~~.

22. (canceled)

2. ~~23.~~ (previously presented): A method as defined in claim ~~21~~ 1 wherein said body fluid is selected from the group consisting of blood, a blood product and cerebrospinal fluid.

3. ~~24.~~ (previously presented): A method as defined in claim ~~21~~ 1 wherein said brain endothelial cell membrane protein is selected from one or more of the group consisting of Thrombomodulin, Glucose Transporter I in the dimeric or tetrameric form, Neurothelin, Gamma Glutamyl Transpeptidase, and P-glycoprotein.

4. ~~25.~~ (original): A method as defined in claim ~~24~~ 3 wherein said brain endothelial cell membrane protein is Thrombomodulin.

5. ~~26.~~ (previously presented): A method as defined in claim ~~21~~ 1 further comprising:
analyzing said body fluid to detect presence and concentration level of a secondary marker protein, said secondary marker protein being from the cell type of one of said myelin basic protein, beta isoform of S100 protein or neuronal specific enolase, whereby the time of onset of a hemorrhagic or ischemic cerebral event can be determined.

6. ~~27.~~ (previously presented): A method as defined in claim ~~26~~ 5 wherein said secondary marker protein has a higher molecular weight than said corresponding myelin basic protein, beta isoform of S100 protein or neuronal specific enolase.

7. ~~28.~~ (previously presented): A method as defined in claim ~~21~~ 1 wherein each of said analyses is carried out on a single sample of body fluid.

8. ~~29.~~ (original): A method as defined in claim ~~21~~ 1 wherein at least one of said analyses is carried out on a first sample of body fluid and at least another of said analyses is carried out on a second sample of body fluid.

9. ~~30.~~ (original): A method as defined in claim ~~29~~ 8 wherein said first and said second samples of body fluid are taken at different time periods.

10. ~~31.~~ (original): A method as defined in claim ~~21~~ 1 wherein a plurality of samples of said body fluid are obtained at predefined time intervals and analyzed and the information from said analyses compared as a function of time whereby the progression of an ischemic or hemorrhagic cerebral event can be determined.

11. ~~32.~~ (original): A method as defined in claim ~~21~~ 1 wherein each of said analyses comprises contacting said body fluid with an antibody which is specific for said protein.

12. ~~33.~~ (original): A method as defined in claim ~~32~~ 11 wherein at least one of said analyses is carried out with an enzyme-labeled immunoassay method.

34-40. (canceled)

13. ~~41.~~ (currently amended): A method for diagnosing an ischemic or hemorrhagic cerebral event comprising:

(a) analyzing a body fluid of a patient to detect the presence and concentration level of four proteins comprising myelin basic protein (MBP), the beta isoform of S100

protein (S100), neuronal specific enolase (NSE) and a brain endothelial cell membrane protein;

(b) comparing the concentration level of each said protein detected in step (a) to specific threshold values to determine the presence of a statistically significant concentration thereof;

(c) assessing patient condition by comparing said presence or absence of statistically significant concentrations of said proteins in accordance with an analytical flow chart; and

(d) determining whether the patient condition assessed in step (c) is an ischemic cerebral event or an hemorrhagic cerebral event, wherein if only said NSE is elevated, or if only said brain endothelial cell membrane protein is elevated, or if S100 is present alone or along with any of NSE, MBP or a brain endothelial cell membrane, then said patient condition is indicative of an ischemic cerebral event; unless MBP is present at a level 200 times normal or greater, or unless S100 and NSE levels are elevated, and MBP and brain endothelial membrane protein levels are normal, then said patient condition is indicative of a hemorrhagic cerebral event.

14. ~~42.~~ (currently amended): The method of claim ~~40 or 41~~ 13 wherein said protein(s) are present at a statistically significant concentration if the concentration of said protein is about two standard deviations above normal levels.

15. ~~43.~~ (currently amended): The method of claim ~~40 or~~ 13 ~~41~~ wherein said brain endothelial cell membrane protein is selected from the group consisting of thrombomodulin, glucose transporter I (dimeric form), glucose transporter I (tetrameric form), neurothelin, gamma glutamyl transpeptidase, and p-glycoprotein.

16. ~~44.~~ (currently amended): The method of claim ~~21, 40~~ 1 or 13 ~~41~~ wherein at least one of said analyses in step (a) is conducted on a first sample of body fluid and at least another of said analyses in step (a) is carried out on a second sample of body fluid.

17. ~~45.~~ (previously presented): The method of Claim ~~44~~ 16, wherein said first sample and said second sample of body fluid are taken at different times.

46. (canceled)

18. ~~47.~~ (currently amended): The method of Claim ~~41~~ 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of only NSE at a statistically significant concentration is indicative that said ~~brain injury~~ cerebral event is a transitory ischemic attack (TIA).

19. ~~48.~~ (currently amended): The method of Claim ~~41~~ 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of NSE and one or more proteins selected from the group consisting of MBP, S100, and a brain endothelial cell membrane protein at a statistically significant concentration is indicative that said ~~brain injury~~ cerebral event is a cerebral infarction.

20. ~~49.~~ (currently amended): The method of Claim ~~41~~ 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of only a brain endothelial cell membrane protein at a statistically significant concentration is indicative that said ~~brain injury~~ cerebral event is a lunar infarction.

21. 50. (currently amended): The method of Claim 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of a brain endothelial cell membrane protein and one or more proteins selected from the group consisting of MBP, S100, and NSE at statistically significant concentrations is indicative that said ~~brain injury~~ cerebral event is a cerebral infarction.

22. 51. (currently amended): The method of Claim 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of MBP at a concentration of greater than about 200 times the normal level is indicative that said ~~brain injury~~ cerebral event is an intracerebral hemorrhage.

23. 52. (currently amended): The method of Claim 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of S100 at a statistically significant concentration is indicative that said ~~brain injury~~ cerebral event is a cerebral infarction or a subarachnoid hemorrhage.

24. 53. (currently amended): The method of Claim 13 further comprising assessing the type of ~~brain injury~~ ischemic or hemorrhagic cerebral event, wherein the presence of S100 and NSE at a statistically significant concentration and the absence of any other markers is indicative that said ~~brain injury~~ cerebral event is a subarachnoid hemorrhage.

25. 54. (currently amended): The method of Claim 1, wherein if ~~MBP, S100, NSE and brain endothelial cell membrane protein are assessed, and~~ only NSE is present, then said ischemic cerebral event is a transitory ischemic attack.

26. 55. (currently amended): The method of Claim 1, wherein if ~~MBP, S100, NSE and brain endothelial cell membrane protein are assessed, and~~ only a brain endothelial cell membrane protein is present, then said ischemic cerebral event is a lacunar infarct.

27. 56. (previously presented): The method of Claim ~~21~~ 1, wherein if S100 is present or if NSE along with any of MBP, S100 or a brain endothelial cell membrane protein are present, or if brain endothelial cell membrane protein, with any one of MBP, NSE, or S100, or if S100 is present with elevated NSE and normal levels of a brain endothelial cell membrane protein, then said ischemic cerebral event is an evolving cerebral infarct.

28. 57. (previously presented): The method of Claim ~~21~~ 1, wherein if MBP is present at a level about 200 times normal or greater, then said hemorrhagic cerebral event is an intracerebral edema.

29. 58. (previously presented): The method of Claim ~~21~~ 1, wherein if S100 and NSE are elevated, and MBP and brain endothelial cell membrane protein levels are normal, then said hemorrhagic cerebral event is a subarachnoid hemorrhage.

30. 59. (previously presented): The method of Claim ~~21~~ 1, wherein if S100 and MBP are elevated, then said hemorrhagic cerebral event is a cerebral edema.

4. **NO EXTENSIONS OF TIME ARE PERMITTED TO FILE CORRECTED OR FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION**, notwithstanding any indication to the contrary in the attached Notice of Allowability (PTO-37).

If the following language appears on the attached Notice of Allowability, the portion lined through below is of no force and effect and is to be ignored[1]:

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to comply will result in ABANDONMENT of this application. ~~Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).~~

[1] The language which is crossed out is contrary to amended 37 CFR 1.85(c) and 1.136. See *"Changes to Implement the Patent Business Goals"*, 65 *Fed. Reg.* 54603, 54629, 54641, 54670, 54674 (September 8, 2000), 1238 *Off. Gaz. Pat. Office* 77, 99, 110, 135, 139 (September 19, 2000).

Similar language appearing in any attachments to the Notice of Allowability, such as in an Examiner's Amendment/Comment or in a Notice of Draftperson's Patent Drawing Review, PTO-948, is also to be ignored.

5. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday – Friday from 8:00AM – 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

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3/23/04

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

03/28/04